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Cardiac Fibrosis in the Athlete: Etiology, Frequency,and Clinical Implications

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Cardiac Fibrosis in the Athlete: Etiology, Frequency, and Clinical Implications

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Myocardial fibrosis (MF)

a common phenomenon in the late stages of diverse cardiac diseases and is a predictive factor for sudden cardiac death

Myocardial fibrosis detected by LGE CMR has been reported to occur in 0% to 50% of asymptomatic athletes. However, the cause and mechanisms of myocardial fibrosis are unclear.

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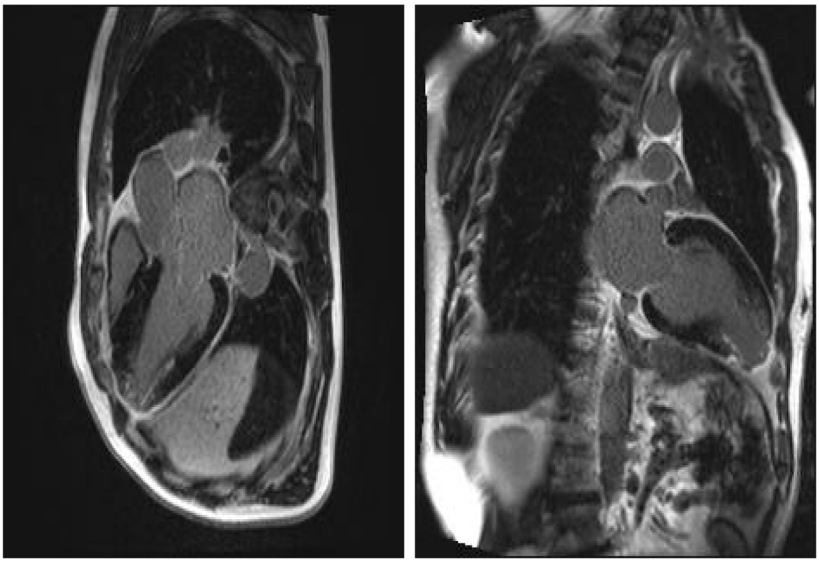
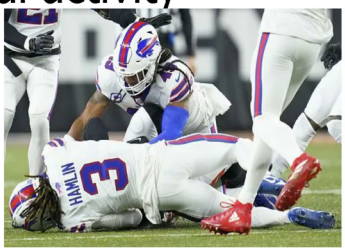
Fibrosis is usually detected in HCMP



The risk of cardiac fibrosis
←Extensive physical activity



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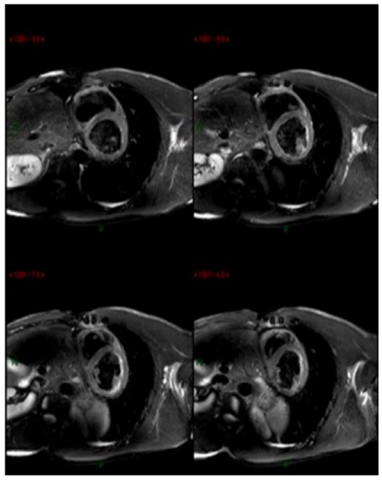
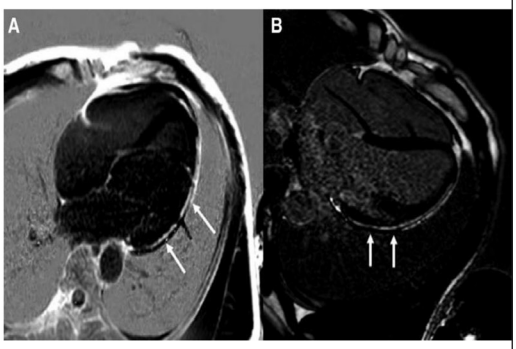
CARDIOVASCULAR IMAGES

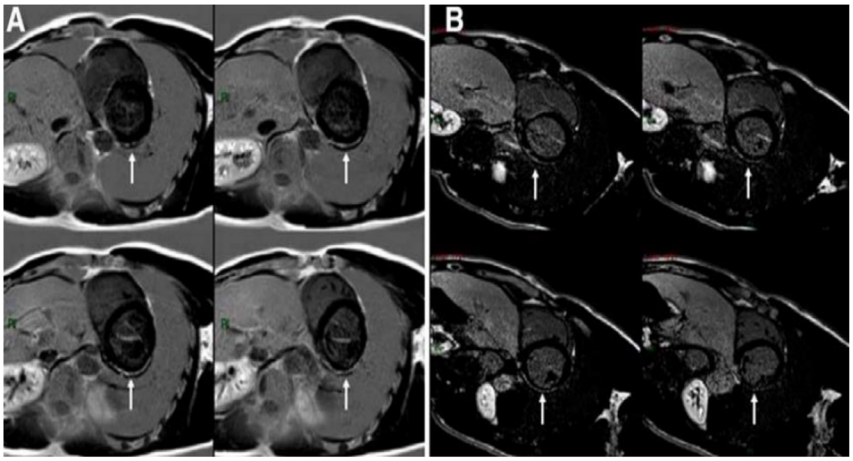
Commotio Cordis in a Professional Soccer Player

Value of MRI in Unraveling Myocardial Damage





Circ Cardiovasc Imaging. 2018;11



Delayed gadolinium-enhanced CMR images in short-axis planes, during hospitalization (A) and at the 2-mo follow-up (B) showing subepicardial enhancement (arrows) in the inferior and lateral walls.

Circ Cardiovasc Imaging. 2018;11

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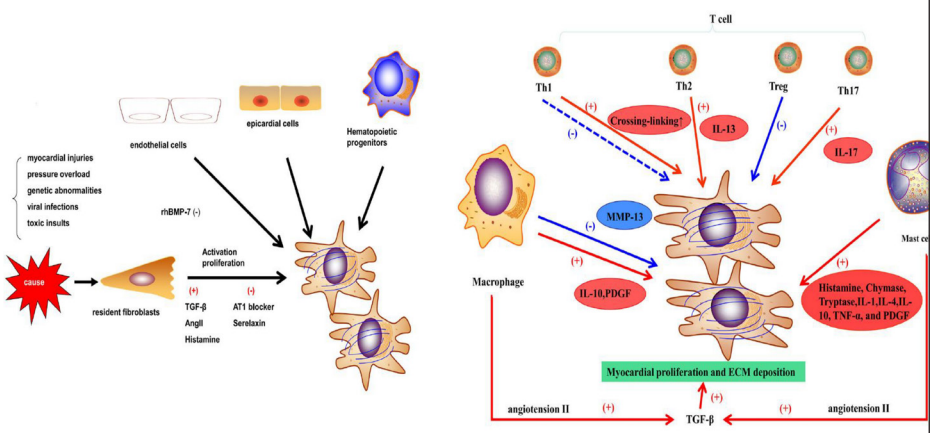
Cardiac disease that cause myocardial fibrosis

The models of myocardial fibrosis	Cardiac diseases
Replacement fibrosis	Myocardial infarction, sarcoidosis, myocarditis, toxic cardimyopathies, chronic renal insufficiency
Reactive interstitial fibrosis	Hypertension, diabetes, non-ischemic dilated cardiomyopathy, hypertrophic cardiomyopathy, sarcoidosis, chronic renal insufficiency
Infiltrative interstitial fibrosis	Amyloidosis, Anderson-Fabry disease

Front. Physiol. 8:238.

Inflammatory response in MF



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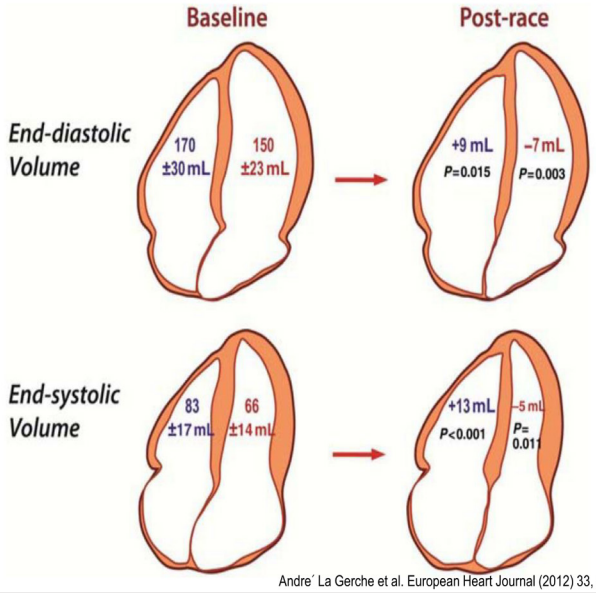
Etiology

Studies have shown that prolonged endurance exercise leads to marked elevation of myocardial necrosis markers, BNP and an increase of inflammatory markers

Until now, just hypothesis - prolonged endurance training, especially without adequate recovery may predispose to myocardial fibrosis

Apart from the risk of arrhythmias, the consequences of myocardial fibrosis may include increased myocardial stiffness and local cardiac dysfunction

Differential effect of prolonged intense exercise on RV and LV volumes



Andre´ La Gerche et al. European Heart Journal (2012) 33, 998–1006

Memo

Risk factor of CV disease in American football player

Study	Year	ASF Population	Participants, N	Key Findings
Baron and Rinsky[19]	1994	Retired Professional	6848	50% increased cardiovascular disease risk in linemen
George et al[30]	2003	Professional	52	34% prevalence of SDB (apnea–-hypopnea index ≥10)
Tucker et al[12]	2009	Professional	504	High prevalence of prehypertension and hypertension (75%)
Selden et al[31]	2009	Professional	69	Cardiometabolic syndrome prevalent among linemen
Hurst et al[32]	2010	Retired Professional	201	Presence of carotid artery plaque similar between retired players and BMI-matched healthy nonathletic controls
Rice et al[33]	2010	Professional	137	19% prevalence SDB (respiratory disturbance index ≥5)
Baron et al[20]	2012	Retired Professional	3439	50% increased cardiovascular mortality for those with playing-time BMI ≥30
Weiner et al[14]	2013	Collegiate freshman	113	High prevalence prehypertension and hypertension (61%) predicted by lineman position
Kim et al[16]	2015	Collegiate freshman	32	Seasonal longitudinal increase in central aortic pulse pressure
Crouse et al[34]	2016	Collegiate freshman	80	High prevalence of prehypertension and hypertension (74%)
Lin et al[17]	2016	Collegiate freshman	87	High prevalence of prehypertension and hypertension (63%)
Kim et al[18]	2017	Collegiate	40	55% prevalence of SDB (apnea–hypopnea index ≥5)

Pathologic CV phenotypes among ASF players

Study	Year	ASF Population	Participants, N	Key Findings
Baggish et al[15]	2008	Collegiate freshman	24	Seasonal longitudinal decrease in echocardiographic measures of diastolic function
Weiner et al[14]	2013	Collegiate freshman	113	31% of linemen developed concentric LV hypertrophy, positive correlation with change in SBP
Kim et al[16]	2015	Collegiate freshman	32	Seasonal longitudinal increase in central aortic pulse pressure, PWV increased compared with older collegiate control group
Lin et al[17]	2016	Collegiate freshman	87	Collegiate linemen with concentric LV hypertrophy were associated with decrements in LV GLS
Kim et al[18]	2017	Collegiate	40	Athletes with SDB demonstrated significant correlation with reduced diastolic function and increased arterial stiffness

ASF indicates American-style football; GLS, global longitudinal strain; LV, left ventricle; PWV, pulse wave velocity; SBP, systolic blood pressure; SDB, sleep-disordered breathing.

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MF Assessment by CMR not echoCG

Can be determined by microscopic examination of tissue samples or by CMR.

Using the administration of a gadolinium-based contrast agent

In the normal heart, the interstitial space undergoes normal "washout" of the contrast agent with no contrast accumulation.

In the presence of myocardial injury or disease, the extracellular space increases leading to delayed "washout" and contrast accumulation. Higher concentration of contrast agent decreasesT1 relaxation time of the studied tissue, thus changing its signal intensity, which appears "bright" (hyperintense) as opposed to the normal myocardium (hypointense).

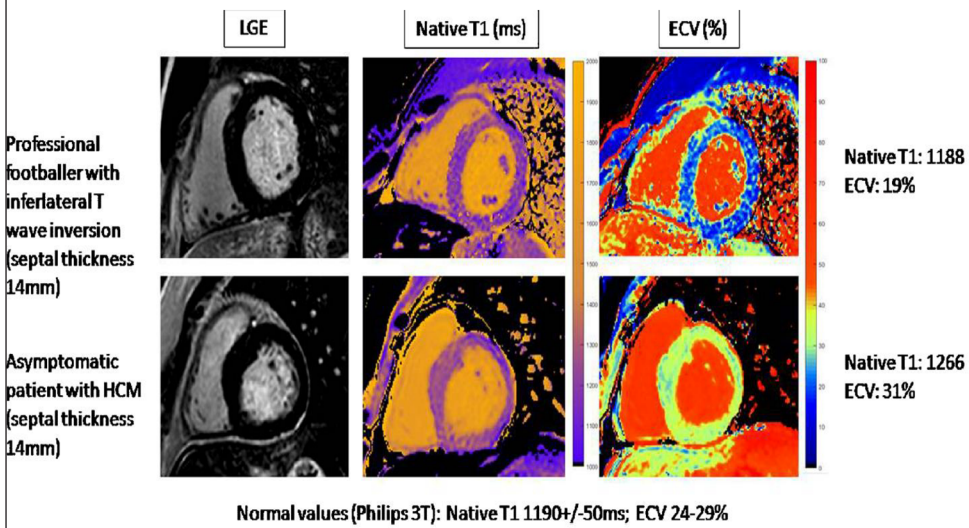

Fig. 1. CMR using T1 mapping and ECV has a potential role in the exclusion of HCM in athletes presenting with LV hypertrophy.

Curr Treat Options Cardio Med (2018) 20: 86

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Table 1. Recent studies indicating prevalence and patterns of myocardial fibrosis in athletic populations using CMR

Study	Size	Exercise type	Age	Pattern	Prevalence	Associated factors
Merghani [45•]	*n* = 152	Masters endurance athletes	54.4 ± 9 years	7% Ischemic pattern 8% non-ischemic pattern	14% male athletes	No relationship between fibrosis and exercise intensity, years of training, or number of competitions
Breuckmann [46]	*n* = 102	'Ostensibly' healthy male runners	61 ± 11 years	5% ischemic pattern 7% non-ischemic pattern	12% prevalence	The event-free survival rate was lower in runners with myocardial LGE than in those without myocardial LGE
Tahir et al.[47••]	*n* = 83	Triathletes	43 ± 10 years	Focal non-ischemic myocardial	17% male athletes	Exercise-induced hypertension and the race distances
Sanchis-Gomar [48]	*n* = 53	11 former 'elite' and 42 amateur-level cyclists or runners	55 ± 15 years	Non-ischemic pattern	4% former 'elite'	No association with any of the biomarkers of fibrosis/remodeling
Wilson [49]	*n* = 12	Competitive endurance veteran athletes	56 ± 6 years	4 veteran athletes with nonspecific cause 1 previous myocarditis 1 silent myocardial infarction	50% of veteran athletes	Number of years spent training, number of competitive marathons and ultra-marathons completed
Schnell [50]	*n* = 7	Asymptomatic athletes recruited during workup of abnormalities on their regular screening examination	26 ± 5 years	Extensive subepicardial LGE predominantly in the lateral wall	100% prevalence as per inclusion criteria	Symptomatic ventricular tachycardia and progressive left ventricular dysfunction

LGE late gadolinium enhancement

MF in triathletes: only men, not women

83 asymptomatic triathletes undergoing >10 training h per week vs. 36 sedentary controls

→ focal nonischemic myocardial fibrosis in 9 of 54 (17%) male triathletes (LGE+) but in none of the female triathletes ($p < 0.05$).

FIGURE 2 Schematic Representation of Fibrosis Localization in LGE⁺ Triathletes

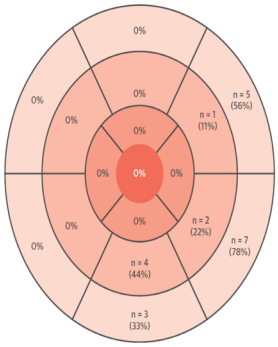
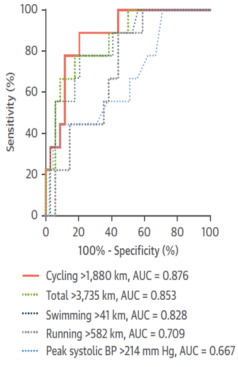


FIGURE 4 Receiver Operating Characteristic Analysis to Identify LGE⁺ Male Triathletes



JACC: CV IMAGING VOL.11. No.9, 2018

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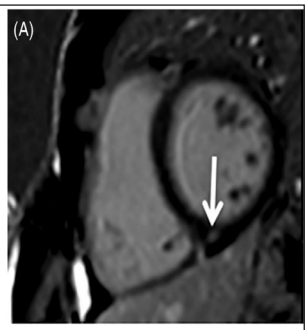
ABLE 1 CMR studies on diffuse fibrosis in athletes with means of T1-mapping technique and ECV calculation

Study	Study size	Training volume/ intensity	Age and sex	LGE vs controls	LGE pattern	T1 vs controls (ms)	ECV vs controls (%)	T1 and ECV in athletes and comments
Malek et al[22]	30 middle age athletes vs 10 controls	Active, median 6 y of ultramarathon running	40.9 ± 6.6, 100% male	27% vs 10%	Nonischemic (insertion point—one in control group, lateral wall)	1200 ± 59 vs1214 ± 32, *P* = .33	26.1 ± 2.9% vs 25.0 ± 2.5%, *P* = .29	Similar T1 and ECV
Pujadas et al[21]	34 veteran athletes vs 11 controls	>10 y of training, still in regular training	48.2 ± 7.5, 100% male	9% vs 0%	Nonischemic(insertion point, lateral wall)	943.6 ± 53 vs 984 ± 37, *P* = .006	25.0 ± 2.0% vs 22.0 ± 2.0%, *P* < .001	Lower T1 and higher ECV, but not after correction for hematocrit
Banks et al[20]	40 athletes vs 8 controls	10 y of competitions, currently 5.2 ± 2.6 h/wk	54 ± 5, 100% male	–	–	1172 ± 29 vs 1187 ± 19, ns	20.7 ± 3.7% vs 17 ± 1.9%, *P* < .05	Similar T1 and higher ECV, values within normal range in both groups
Gormeli et al[17]	46 athletes vs 41 controls	Two groups > and <5 y of sport activity, around 8.6-9.5 ± 2.5 h/wk	24.5 ± 3.05, 62.2% male	–	–	1268 ± 48 vs 1180 ± 27, *P* < .001	–	Higher T1, no ECV calculated
Treibel et al[23]	50 athletes vs 30 healthy volunteers	>10 endurance events in lifetime	42 ± 14 y, 80% male	Those with infarct pattern not included, other types not reported		–	26.2 ± 2.7% in young athletes vs 28.0 ± 2.9%	Lower ECV
Tahir et al[19]	83 athletes vs 36 controls	>3 y of competitions, >10 h/wk	43 ± 10 y, 65% male	17% male, 0% female vs 0% ns	Nonischemic (inferolateral, insertion points)	Male 990 ± 28 vs 1014 ± 28,*P* < .01 Female 1015 ± 25 vs 1059 ± 22, *P* < .0001	Male 24.8 ± 2.2% vs 24.0 ± 3.0, ns Female 27.8 ± 1.9% vs 28.9 ± 3.3, ns	Lower T1 and similar ECV Athletes with LGE had higher remote myocardium ECV
McDiarmid et al[16]	30 athletes vs 15 controls	Athletes committing on regional, national, or international level	31.7 ± 7.7 y, 100% male	3% vs 0%	Nonischemic (postmyocarditis pattern)	1178 ± 32 vs 1202 ± 33, *P* = .02	22.5 ± 2.6% vs 24.5 ± 2.2%, *P* = .02	Lower T1 and ECV
Mordi et al[18]	21 athletes with depressed LVEF vs 21 controls	>6/h per wk of intensive aerobic exercise at an amateur level	45.9 ± 10.7 y, 100% male	9.5% vs 0%	Nonischemic (insertion points)	957 ± 32 vs 952 ± 31, ns	26.3 ± 3.6% vs 26.2 ± 2.9, ns	Similar T1 and ECV

Insertion point fibrosis



- most often, limited to the inferior insertion point
- M/C observed pattern in athletes irrespective of age

: 20~30% prevalence

- correlated with a cumulative training load and training intensity

may reflect the time of pressure and/or volume overload present in the RV during intensive exercise → tension on the insertion points and may lead to microinjuries visible later as spots of LGE in that location

- seems both age and training related and therefore may occur earlier in athletes

- Has been also observed in around 10% of otherwise healthy elderly individuals and may form one of the elements of an aging heart

Clin Cardiol. 2020;43:882–888

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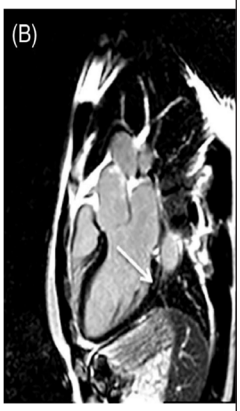
Inferolateral or septal nonischemic fibrosis



less often observed in athletes than insertion point fibrosis

Has been previously noticed in Fabry disease

An acute or healed myocarditis

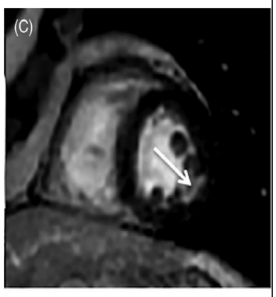
Small, linear sub-epicardial or mid-myocardial areas of LGE in

the inferolateral segments or in the interventricular septum

Intensive, prolonged exercise → affect immune resistance in the short period after intensive exercise, which if combined with seasonal infections may predispose athletes to myocarditis

Clin Cardiol. 2020;43:882–888

Ischemic fibrosis



has been reported predominantly in veteran athletes(>50Y.O.)

the prevalence of common CV risk factors in Olympic athletes

: surprisingly high

- including 0.3% of hyperglycemia,

3.8% of hypertension, 8% of smoking habit, 18% of positive family history, 25% of increased waist circumference, and 32% for dyslipidemia

→endurance athletes had generally low CV risk profile,

but one to two risk factors were still present in 50% of them and 2% of them had three to four risk factors

Clin Cardiol. 2020;43:882–888

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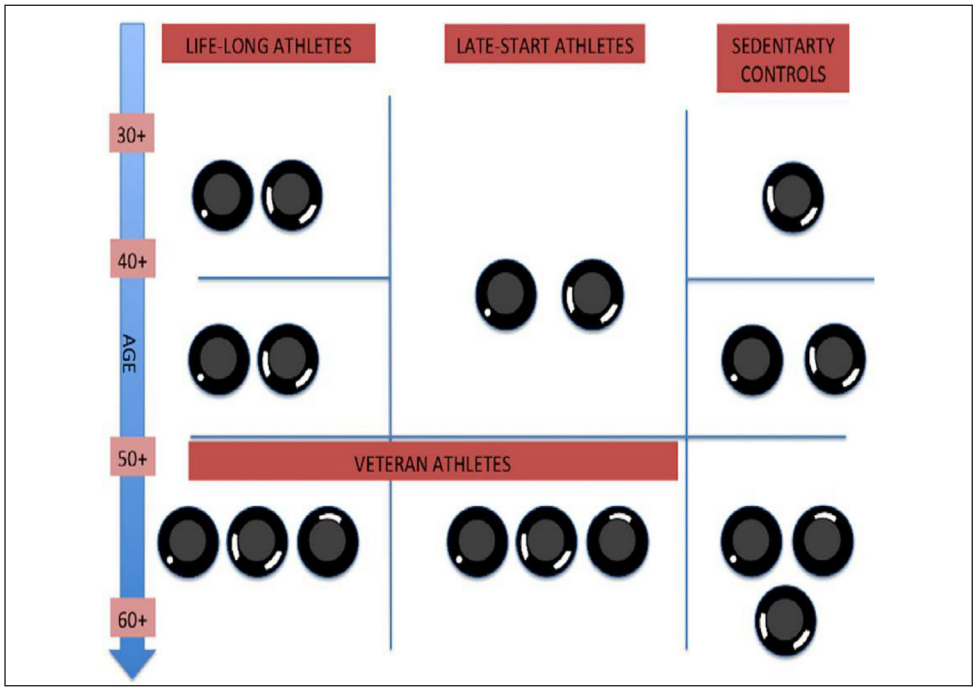

	CMR characteristics
Athlete's heart	Fibrosis: Possible insertion point LGE, normal or reduced T1 time and ECV Other features: Symmetric enlargement of all heart chambers (balanced chamber mild dilatation), high bilateral stroke volumes, concentrically increased myocardial thickness usually up to 13 mm
HCM	Fibrosis: Mid-myocardial LGE in the hypertrophied segments, increased T1 time and ECV Other features: Asymmetric hypertrophy > 13 mm, small LVEDd< 54 mm, more prominent left atrial enlargement, multiple myocardial clefts/crypts
DCM	Fibrosis: Nonischemic patterns of LGE in the LV, increased T1 time and ECV Other features: LVEDd> 60 mm, increased LV volume asymmetrically to other chambers, reduced LVEF not significantly increasing or decreasing during exercise
ARVC	Fibrosis: Nonischemic patterns of LGE in the LV Other features: Regional RV wall akinesia/dyskinesia or dyssynchrony plus RVEDVi meeting major TFC for ARVC or RVEF < 40%, disproportionally larger RV than LV
LVNC	Fibrosis: Nonischemic patterns of LGE in the LV Other features: Noncompacted to compacted layer ratio >2.3 (measured in long-axis view avoiding the apex), reduced thickness of the compacted layer, involvement of several LV segments, LVEF < 50%

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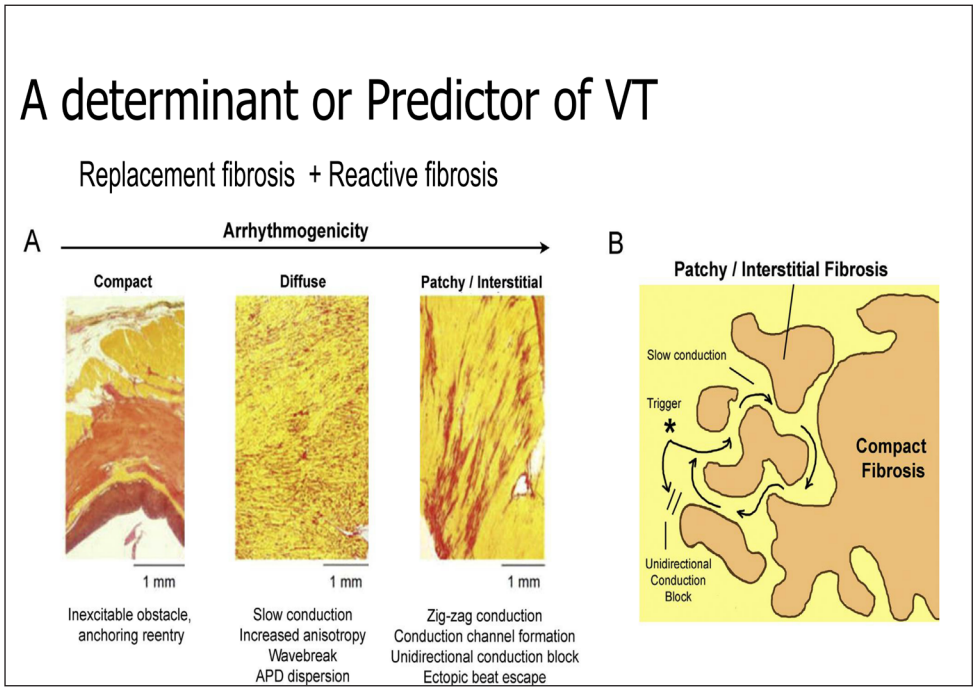

Table 1 – Methods for the non-invasive assessment of ventricular fibrosis in the clinical setting.

Methods		Fibrosis markers
Electrocardiography	Fragmented QRS in normal and wide QRS	– Presence of an additional R wave (R′), or notching in the nadir of R or S wave, or presence of more than one R′ (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory – More than 2 notches on the R or S wave in patients with wide QRS
Echocardiography	Integrated backscatter	– Augmented regional ultrasonic reflectivity
	Speckle-tracking strain imaging	– Abnormal global/regional longitudinal strain– Abnormal mechanical dispersion
Biomarkers	Collagen turnover biomarkers	– Increased PICP/PIIINP ratio – Increased MMP-9/TIMP-1 ratio
Cardiac magnetic resonance	Late gadolinium enhancement	– Detection of patchy/interstitial fibrosis as hyperenhanced bright areas– Regional patterns of fibrosis:– **ICM**: fibrosis is usually sub-endocardial or transmural in the distribution of an occluded coronary artery– **NICM**: fibrosis is patchy and mid-myocardial or sub-epicardial– **HCM:** dense areas of replacement fibrosis usually in hypertrophied regions
	T1 mapping	– Detection of diffuse myocardial fibrosis as shorter T1-time areas
Nuclear imaging	SPECT	– Perfusion defects
	PET	– Metabolism-perfusion mismatch

HCM, hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; MMP-9/TIMP-1, matrix metalloproteinase 9/ tissue inhibitor of MMP 1; NICM, nonischemic cardiomyopathy; PET, positron emission tomography; PICP/PIIINP, precollagen type I carboxyterminal peptide/precollagen type III aminoterminal peptide; SPECT, single photon emission computed tomography.

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Clinical implication of asymptomatic MF

Not established but, a proposal of the following management strategy

Only the detection of small insertion point fibrosis does not seem to require further evaluation.

Presence of fibrosis extending beyond the insertion points in the interventricular septum or fibrosis elsewhere in the myocardium regardless of its pattern should prompt further evaluation, especially in the younger athlete age group.

The index of suspicion, regarding potential cardiac disease, should increase if abnormal ECG or the presence of arrhythmias accompanies the detection of fibrosis.

Summary

Increased availability and use of CMR is likely to identify small volume of scar of uncertain significance in a considerable proportion of athletes.

CMR should be reserved for individuals with high index of suspicion for cardiac disease, including athletes with clinical symptoms or abnormalities on first-line investigations, as it may elucidate diagnosis and direct management.

Some combination of available techniques and clinical adoption of new cutting edge methods may lead to a precise appraisal of fibrosis amount and texture, and the direct testing of fibrosis link with ventricular arrhythmias in the single patient.

Memo

To achieve success, whatever the job we have, we must pay a price.

by *Vince Lombardi*

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